**DYNAMIC ASSESSMENT OF PATIENT-REPORTED CHRONIC DISEASE OUTCOMES**

**RELEASE DATE:** November 18, 2003

**RFA Number:** RFA-RM-04-011 (formerly RFA-AR-04-007, see NOT-OD-04-008)

Department of Health and Human Services (DHHS)

**PARTICIPATING ORGANIZATION:**
National Institutes of Health (NIH)
(http://www.nih.gov)

This RFA is developed as an NIH Roadmap initiative (http://nihroadmap.nih.gov/). All NIH Institutes and Centers participate in Roadmap initiatives. The RFA will be administered by the NIAMS on behalf of the NIH.

CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBERS: 93.846

LETTER OF INTENT RECEIPT DATE: February 22, 2004
APPLICATION RECEIPT DATE: March 22, 2004

THIS RFA CONTAINS THE FOLLOWING INFORMATION



PURPOSE OF THIS RFA

The Institutes and Centers of the National Institutes of Health seek proposals for innovative approaches to measuring patient-reported outcomes (PROs) that will meet the needs of clinical researchers across a wide variety of chronic disorders and diseases. This RFA solicits two types of applications; (1) individual research proposals, with added

concept proposals for network-wide collection of self-report data on specific domains of patient-reported outcomes, symptoms, or quality of life in large and diverse samples, and (2) proposals for a statistical coordinating center that will serve as a data repository, conduct analyses, and develop a computerized system to administer, collect, and report PRO data. The principal investigators of each project will become members of a network - Patient-Reported Outcomes Measurement Information System (PROMIS)- to be established immediately following award. Proposals will be funded as cooperative agreements, and PROMIS investigators will work collaboratively to refine and coordinate proposed domains to be measured, to collect, manage, and evaluate the data, and to develop a computerized system that administers dynamic questionnaires (i.e., computerized adaptive tests, CAT), collects and manages PRO data, and creates reports of health-related quality of life status for clinical researchers, patients, and health care providers. The broad objectives of the RFA are to (1) develop and test a large bank of items measuring PROs; (2) create a computerized adaptive testing system that will allow for efficient, psychometrically robust assessment of patient-reported outcomes in clinical research involving a wide range of chronic diseases, and (3) create a publicly-available system that can be added to and modified periodically and that will allow clinical researchers to access a common repository of items and CAT. This initiative addresses the need, identified as a high priority in the NIH Roadmap process, for improved assessment of symptoms and other patient-centered outcomes in clinical research.

## RESEARCH OBJECTIVES

### Background

Conventional clinical and functional measures of disease status do not fully capture the ways in which chronic diseases and their treatment affect individuals. Many aspects of patients' subjective experience, such as symptom severity and frequency, emotional and social well-being, and perceived level of health and functional ability are important targets for disease intervention that are not measured by x-rays or laboratory results. Measurement of patient-reported outcomes is particularly important in clinical trials, in which changes in clinical measurements or imaging results may not translate into important benefit to the patients, or in trials in which two treatments may be comparable in limiting or curing disease but have different adverse effect profiles differentially affecting symptoms, functioning, or other aspects of patients’ quality of life.

The last several decades have seen a proliferation of tools to measure symptoms, quality of life, functional status, emotional status, and general perception of health. Although many of these instruments have good demonstrated reliability and validity, there are many limitations to current measurement approaches. One critical disadvantage is the inability to compare results of different studies when different measurement tools are used, as these instruments will have non-comparable or non-combinable scores because each scale may use a different number of items, different response options, different reference periods, or different item content. For example, progress in clinical pain research is slowed by the use of various pain measurement scales that are not directly comparable. The length and complexity of questionnaires and batteries can also

be problematic, creating a level of respondent burden that hampers recruitment, results in too much missing data, or is detrimental to response validity and reliability. The clinical outcomes research enterprise would be enhanced greatly by the availability of a psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics. New computer technologies and advances in modern measurement theory make it possible to develop, maintain, and add to item banks, to compare items and conduct statistical modeling of responses, and to create computerized adaptive testing that allows item subsets to be tailored to the individual without loss of scale precision or content validity. Ultimately, such a system would also be useful in clinical practice to assess response to interventions and to inform modification of treatment plans.

This initiative will establish a collaborative (PROMIS) of investigators to improve measurement of patient-reported outcomes. The network will focus on the collection of self-report data from a diverse population of individuals, including racial and ethnic minorities, having a variety of chronic diseases. PROMIS will support a comprehensive and integrated approach to data collection, storage, and management, and will have a Statistical Coordinating Center that will manage analyses and generation of item banks and computerized adaptive testing systems.

Specific research objectives are:

o To identify a core set of questions, derived primarily from existing, commonly-used instruments and supplemented by new and revised items, that will address the most common or salient dimensions of patient-relevant outcomes for the widest possible range of chronic disorders and diseases, and to collect responses to these items in a large, diverse sample. Domains of interest include, but are not limited to, self reported: symptoms, physical functioning, participation in activities, social functioning; cognitive functioning, and emotional status. Of special interest are the assessment of pain severity, frequency, and impact and the assessment of fatigue as clinical outcomes of high importance to many people suffering from chronic diseases.

o To compare the performance of specific items, instruments, and models across diverse clinical populations, and to develop common metrics by which scores on new and existing instruments can be standardized and/or linked;

o To use methods made available by modern measurement theory (i.e., item response theory modeling), cognitive aspects of survey methodology, qualitative research methods, and other sophisticated approaches to create an item bank for each domain measured;

o To develop a new computerized adaptive testing (CAT) tool that can be used across a number of delivery platforms in a variety of clinical settings and with a wide range of chronic disease populations. The CAT will select questions from the item banks to deliver tailored instruments with enhanced sensitivity and precision, reduced floor and ceiling effects, and reduced response burden;

o To develop a web-based, user-friendly repository that can be updated periodically, and to which data can be added from additional research. This resource, the PROMIS, will be used to administer CAT, collect and manage data, and provide instant reports to clinical researchers and patients (and ultimately to health care providers, as appropriate);

o To develop a plan to maximize acceptance of this new measurement tool in the clinical research community and in health-care settings. This plan should involve soliciting input from clinical researchers, clinicians, patients, and others throughout the study cycle.

o To perform feasibility studies to evaluate the success of the CAT system and public use item repository, and to use feasibility study results to enhance the PROMIS;

o To develop a plan to establish a public-private partnership to sustain the repository, ensure scientific excellence, improve future data collection activities by updating items as necessary, adding new items or new domains, testing and adapting the system in new populations, and extending the reach of this system to be used across a variety of media as technology allows. Approaches for training potential clinical research users should be explored.

Approximate Timetable

Year 1: The Primary Research Sites (PRSs) and the Statistical Coordinating Center (SCC) will work collaboratively to choose the specific domains, constructs, existing instruments, and items to be analyzed for possible administration to diverse patient populations in later years; obtain IRB approvals, conduct focus groups, develop new items, conduct cognitive interviews with target populations on both existing and new items, discuss CAT development, collect pilot data, and develop and test data collection and reporting procedures. Interact with potential future users of the item bank and CAT (i.e., clinical researchers, clinicians, and patients) to facilitate development of the most useful protocols and research products.

Year 2: Adopt core items for data collection by the PRSs; develop software, as necessary, for questionnaire administration and data collection; develop interface for CAT; and initiate large-scale data collection.

Year 3: Continue data collection and initiate ongoing data analysis for use in alpha version of CAT.

Year 4: Complete data analyses, including assessing the psychometric properties of the scales, assessing measurement equivalence through tests for differential item functioning, and conducting comparisons among existing PRO questionnaires and developing linking metrics to combine or compare scores; conduct second test of CAT (beta test); and then finalize the CAT system.

Year 5: Evaluate the feasibility and utility of the CAT and the public domain

item bank; pilot test clinical researchers' use of CAT and the item bank; develop strategies and form partnership(s) to provide for ongoing development and maintenance of the item bank and associated CAT technology.

Organization of PROMIS

PROMIS will be a cooperative network consisting of several Primary Research Sites (PRSs) and a single Statistical Coordinating Center (SCC). A Steering Committee will establish the procedures for the function of the network, as outlined in the "Steering Committee" section below. In addition, the NIH will establish an independent Scientific Advisory Board (SAB) to provide oversight of PROMIS and each PROMIS component.

Primary Research Sites. PRS applicants will propose both a specific, independent research project and two concepts for projects to be adopted by the network as a whole. Projects proposed by PRS applicants for adoption by the network should directly address the specific RFA objectives listed above. The independent project should address, or be related to, one or more aspects of the network specific objectives listed above. After the network is established, the principal investigator of the PRS may choose to revise aspects of the independent project to take advantage of opportunities provided by the other PROMIS sites, and/or to increase the relevance or contribution of the independent project to the network. Examples of topics for the independent project include, but are not limited to:

o Studies of proposed core patient-reported outcomes in special populations or comparisons between populations differentiated by racial, ethnic, or other sociodemographic characteristics, diagnosis, disease-related characteristics, or treatment;

o Studies of the psychometric properties of one or more domains of patient-reported outcomes different from those proposed by the applicant for adoption by the entire network;

o Investigation of minimum clinically important differences in proposed core measures and other domains of patient-reported outcomes;

o Investigation of health preferences or health utilities, including developing the means to compare the burden associated with different health states, to compare the relative importance to patients and the general community of movement from one health state to another, and to create a single health summary score to support cost-effectiveness analysis;

o Development, testing, or comparison of different methods or technologies for collecting patient-reported outcomes;

o Studies involving translation and testing of non-English instruments, adapting instruments for cultural sensitivity or relevance, or of adapting instruments for low-

literacy or for physical or cognitive handicaps, using proposed core and other instruments.

o Studies relating self-report data to behavioral or physiological data, including data collected using “real time” methods and technologies;

o Studies of longitudinal disease course and treatment outcomes using proposed core measures and other domains of patient-reported outcomes.

Further instructions regarding elements to be included in PRS applications are listed in the section “SUPPLEMENTAL INSTRUCTIONS.”

Statistical Coordinating Center. The SCC will provide and manage a secure, customizable, coordinated data management system for collection, storage, and analysis of data to be collected by the PRSs. With the guidance of the PRSs and the Steering Committee, the SCC will create the core PRO questionnaires to be administered across all PRS sites, in both paper and computer-based formats. The SCC will be primarily responsible for analyzing the data using item response theory (IRT) modeling and other sophisticated psychometric approaches, and for creating item banks. The item banks will serve as the foundation for the further development of tailored short-form instruments and computerized adaptive testing techniques (CAT). The item banks, short forms, and CAT will be made widely available to clinical researchers as a web-based application (or downloadable to computer devices), and the SCC will develop training for clinical researchers in the use of this resource. Instructions regarding elements to be included in SCC applications are listed in the section “SUPPLEMENTAL INSTRUCTIONS.” In addition, SCC applicants may propose up to two separate research plans for complementary research projects entailing data collection techniques, advances in psychometric or statistical methodology or measurement, or other topics related to this RFA.

Steering Committee. The Steering Committee (SC) will function as the main governing board of all grants awarded under this RFA, and will be the committee through which the NIH interacts and collaborates with the facilities. Voting membership includes the NIH Science Officer(s) (no more than 40% of total votes) and the PI of each awarded cooperative agreement. Additional committee members may be added by action of the Steering Committee. Other NIH staff may attend Steering Committee meetings when their expertise is required for specific discussions.

Scientific Advisory Board. This committee ensures coordination among funded projects and evaluates their progress in relation to the goals of this initiative. The Scientific Advisory Board will use its knowledge of the activities of all of the participating facilities to ensure adequate investigation, communication, and sharing, and will evaluate and make recommendations regarding coordination of awardee activities and regarding other

related activities that may be developed in the future.

It will be the responsibility of the Scientific Advisory Board to make recommendations that will lead to exchanging research tools, research resources, adopting common policies on data sharing, creating item banks, and other activities that will make the resources developed of maximal utility to the scientific community.

The SAB will be appointed by the NIH, and will consist of approximately 6 scientists (advisors) who are not affiliated with any of the funded sites. These advisors will be selected for their broad expertise in relevant topics. The SAB will meet at least once each year. A schedule for subsequent meetings will be prepared at the first meeting.

The NIH will select one member to be the SAB chair, after considering the SAB recommendations. The chair will schedule the first meeting, and will be responsible for developing meeting agendas and chairing the meetings. Additional SAB members may be added by an action of the original committee members. The SC Chair and Science Officer(s) will attend SAB as non-voting members and will act as representatives of SC. Other NIH staff and Steering Committee members may attend SAB meetings when their expertise is required for specific discussions.

## MECHANISM OF SUPPORT

This RFA will use the NIH U01 award mechanism. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is September, 2004.

This RFA uses just-in-time concepts. It also uses the non-modular budgeting formats. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

The NIH U01 is a cooperative agreement award mechanism in which the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award". The initial period of support for a U01 will be five years.

## FUNDS AVAILABLE

The NIH intends to commit approximately $5,000,000 in FY 2004 to fund three to six new grants for Primary Research Sites and one new grant for a Statistical Coordinating Center in response to this RFA. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size of each award will also vary. Although the financial plans of the NIH provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

## ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic institutions/organizations
- Faith-based or community-based organizations
- Foreign institutions are not eligible to apply

## INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with his or her institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

## SPECIAL REQUIREMENTS

PROMIS will be a collaborative effort requiring frequent interactions among awardees. All awardees will cooperate fully in the planning and implementation of collaborative network projects designed to address the research objectives described in this RFA. Data on core items from the collaborative projects will be pooled for joint analysis, interpretation, and publication by PROMIS investigators in accordance with policies and procedures established by a Steering Committee (SC) to be formed shortly following award.

All awardees are required to participate in meetings and/or conference calls, possibly quarterly, to discuss and review scientific and technical aspects of implementation, analyses, and presentation of data. At least one investigator from each award, preferably the PI, must attend these meetings. Up to three additional key personnel from each award,

if appropriate, may attend. Applicants should plan for 4 trips per year and budget accordingly.

To address the joint interests of the government in the availability of, and access to, the results of publicly funded research, the NIH requires applicants who respond to this RFA to propose detailed plans for sharing the research resources generated through the cooperative agreement. The resource-sharing plan will include providing the wider scientific community access to the data repository and CAT with appropriate timeliness and mileposts. For example, software development should include plans and a timeline for alpha testing, beta testing, production release, interface development, bug reporting, integration with other codes, extension to multiple platforms, etc. Data sharing will be as important as software sharing. All awards made under this RFA are subject to the Final NIH Statement on Sharing Research Data (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html).

Intellectual Property Rights

The NIH is interested in ensuring that the research resources developed through this RFA become readily available to the research community. The majority of transfers to not-for-profit entities should be implemented under terms no more restrictive than the Uniform Biological Materials Transfer Agreement (UBMTA). In particular, recipients are expected to use the Simple Letter Agreement provided at http://www.nih.gov/od/ott/RTguide_final.htm, or another document with no more restrictive terms, to readily transfer unpatented tools developed with NIH funds to other recipients for use in NIH-funded projects. Commercialization option rights, royalty reach-through, or product reach-through rights back to the provider are inappropriate. No fees should be collected to use the instruments or gain access to the PROMIS.

Principles and guidelines for recipients of NIH research awards on obtaining and disseminating biomedical research resources can be found at http://www.nih.gov/od/ott/RTguide_final.htm. A reasonable time frame for release of materials should be specified in the application and will be considered during the review of the plan for sharing.

Cooperative Agreement Terms and Conditions of Award

Patient-Reported outcomes Measurement Information System (PROMIS)

The following Terms and Conditions will be incorporated into the award statement. The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies:

The administrative and funding instrument used for this program is the cooperative agreement (U01),an "assistance", rather than an "acquisition", mechanism, in which

substantial NIH scientific and/or programmatic involvement with the awardee is anticipated during the performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by involvement in and otherwise working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility, or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the research will be shared among the awardees and the NIH Science Officer(s) as described below.

1. Principal Investigator Responsibilities

Primary Research Sites (PRSs): The Principal Investigator will have primary authority and responsibility for the independent project and for contributions to the network, including research design, protocol development, setting milestones, and analysis of data, as agreed upon by the Steering Committee. The PI will accept and implement the common guidelines and procedures approved by the Steering Committee. In accordance with policies and procedures established by the Steering Committee, core data from the collaborative projects will be pooled for joint analysis, interpretation, and publication by PROMIS investigators; periodic progress reports will be submitted in a standard format. During the first year of the award, the Steering Committee will discuss and agree upon policies and procedures regarding its degree of involvement with the independent projects (e.g., communication regarding independent project activities and progress, publication of independent project results).

Statistical Coordinating Center (SCC): The Principal Investigator will have primary authority and responsibility for management and analysis of data, creating an item bank, developing a computerized adaptive testing (CAT) tool, and developing training for clinical researchers, as agreed upon by the Steering Committee. In accordance with policies and procedures established by the Steering Committee, core data from the collaborative projects will be pooled for joint analysis, interpretation, and publication by PROMIS investigators; periodic progress reports will be submitted in a standard format, and item banks and tools will be released according to the approved plans for sharing research resources generated through the award.

2. NIH Science Officer(s)

The NIH Science Officer(s) named in the Notice of Award will have substantial scientific/programmatic involvement during the conduct of this activity through technical assistance, advice, and coordination above and beyond normal program stewardship for grants. This involvement includes functioning as a partner with the PIs and providing significant input in the planning and conduct of the research, to include working with the Principal Investigators in finalizing the set of items to be tested and the testing methodology, planning for data analysis, interpreting data and, if warranted, in co-

authoring manuscripts for publication. The Science Officer(s) will also serve as scientific liaison between the awardees and other NIH program staff, and retain the option to recommend re-allocating NIH support among awardees as scientific goals evolve. The Science Officer(s) must be informed of all major interactions of members of PROMIS.

3. NIH Program Director

THE NIH will appoint a Program Director who will have responsibility for normal program oversight and stewardship of the award. The Program Director will appoint the Steering Committee chair based on recommendations from the Steering Committee members, serve as a non-voting member of the Steering Committee, carry out continuous review of all activities to ensure objectives are being met, and have the option to recommend withholding support to a participating institution if technical performance requirements are not met.

4. Collaborative Responsibilities

Steering Committee (SC): The NIH will interact and collaborate with the facilities principally through the Steering Committee, which will function as the main governing board. Voting membership includes the PI of each awarded cooperative agreement and one or more NIH Science Officers(s) (no more than 40% of total votes). Additional committee members may be added by action of the Steering Committee. Other NIH staff may attend Steering Committee meetings when their expertise is required for specific discussions.

The Science Officer(s) will schedule the first meeting and set the agenda, following which the Chair of the committee will be responsible for developing meeting agendas and chairing meetings. The Steering Committee will meet at least twice per year, but may use video or teleconferencing rather than face-to-face meetings, at the discretion of the committee members. The purpose of these SC meetings is to identify core items to be used in developing item banks; share scientific information; assess scientific progress; identify new research opportunities; discuss strategy and potential avenues of collaborations (such as with industry, private foundations and/or NIH intramural scientists); establish priorities that will accelerate the transfer of item banks and CAT to the clinical research community; reallocate resources; and conduct the business of the cooperative research program. The Steering Committee will develop the process and review procedures for handling proposed additional studies with the funds reserved for this purpose. The use of these funds will be restricted and must be reviewed and approved by the Steering Committee and then recommended to, and approved by, the NIAMS for release from the individual U01 awards. Decisions will be made by a majority vote of a quorum, with an attempt at consensus.

Scientific Advisory Board (SAB). The Scientific Advisory Board will be make recommendations that will lead to exchanging research tools, research resources, adopting common policies on data sharing, creating item banks, and other activities that will make the resources developed of maximal utility to the scientific community. This committee ensures coordination among funded projects and evaluates their progress in relation to the goals of this initiative. The Scientific Advisory Board will use its knowledge of the activities of all of the participating facilities to ensure adequate investigation, communication, and sharing, and will evaluate and make recommendations regarding coordination of awardee activities and regarding other related activities that may be developed in the future.

The SAB will be appointed by the NIH, and will consist of approximately 6 scientists (advisors) who are not affiliated with any of the funded sites. These advisors will be selected for their broad expertise in relevant topics. The SAB will meet at least once each year. A schedule for subsequent meetings will be prepared at the first meeting. The NIH will select one member to be the SAB chair, after considering the SAB recommendations. The chair will schedule the first meeting, and will be responsible for developing meeting agendas and chairing the meetings. Additional SAB members may be added by an action of the original committee members. The SC Chair and Science Officer(s) will attend SAB as non-voting members and will act as representatives of SC. Other NIH staff and Steering Committee members may attend SAB meetings when their expertise is required for specific discussions.

5. Milestones and Evaluations

The NIH Program Director will review the progress of the network and the Steering Committee annually to assure that satisfactory progress is being made in achieving objectives. During the first year of funding, and during subsequent years if deemed necessary by the Program Director, reviews may be more frequent. Should problems arise in the conduct of the study, the NIH Program Director may require that the awardee submit quarterly reports on progress and fiscal matters.

The progress report will be the standard annual NIH progress report (Form 2590). The awardees' yearly milestones will be provided to the Steering Committee and the SAB. The milestones should be adjusted annually at the award anniversary dates, both to incorporate a group's scientific accomplishments and progress, as well as to reflect Steering Committee and SAB recommendations. Following the evaluation of milestones, NIH program staff may recommend augmenting any project or reducing or withholding funds for any project that substantially fails to meet its milestones or to remain state-of-the-art.

6. Arbitration

Any disagreement that may arise on scientific/programmatic matters (within the scope of the award), between award recipients and the NIH may be brought to arbitration. An

arbitration panel will consist of one person selected by the Principal Investigators, one person selected by the NIH, and a third person selected by both NIH staff and the Principal Investigators. The decision of the arbitration panel, by majority vote, will be binding. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

**WHERE TO SEND INQUIRIES**

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research and financial or grants management issues:

o Direct your questions about scientific/research issues to:

Deborah N. Ader, Ph.D.
Director, Behavioral and Prevention Research Program
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20872-4872
Telephone: (301) 594-5032
Fax: (301) 480-1284
Email: aderd@mail.nih.gov

Lawrence J. Fine, M.D., Dr.PH
Medical Advisor, OBSSR-NIH
Room 256, Building One
One Center Drive
Bethesda, MD 20892
Telephone: 301-435-6780
Fax: 301-402-1150
Email: FineL@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Melinda Nelson
Grants Management Officer
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20872-4872 Telephone: (301) 594-3535
Fax: (301) 480-5450
Email: nelsonm@mail.nih.gov

## LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research
o Name, address, and telephone number of the Principal Investigator
o Names of other key personnel
o Participating institutions
o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Deborah N. Ader, Ph.D.
Director, Behavioral and Prevention Research Program
NIAMS
One Democracy Plaza
6701 Democracy Boulevard, Suite 800, MSC 4872
Bethesda, MD 20872-4872 Telephone: (301) 594-5032
Fax: (301) 480-1284
Email: aderd@mail.nih.gov

## SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo,
Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

## SUPPLEMENTARY INSTRUCTIONS

Specific Instructions for Primary Research Site Applications

Independent Projects: Applicants should propose objectives, hypotheses,

measures, and statistical analysis plans for their independent projects following the usual PHS 398 instructions, and the Research Plan (Sections A-D) for this portion of the application will be a maximum of 25 pages in length. Applicants should explicitly discuss how the independent project is relevant and complementary to the RFA objectives. Section E., Human Subjects, has no page limit.

Network Projects: The independent project research plan must be followed with 2 concept proposals to be considered for adoption by PROMIS. An additional fifteen pages, total (not including budget information), will be allowed for these proposals and for a statement of capability to contribute to the network. Proposals for PROMIS projects should include the following:

o Aims - hypotheses and associated proposed core measures (i.e., measures to be used by all PROMIS sites), and additional important variables to be measured, such as co morbidity and sociodemographic characteristics;

o Relevance – a statement of the scientific relevance and the importance of proposed measures and related domains for improving measurement of patient-reported outcomes in diverse populations;

o Requirements and Feasibility – e.g., need and ability to conduct focus groups to determine constructs, instruments, and items to include; ability to carry-out assessments of patient populations using a variety of methods and technologies; and ability to apply cognitive aspects of survey methodology to assess patients' comprehension of items and response categories. Applicants may propose development and testing of innovative systems;

o Statement of Capability - demonstration of a supportive institutional environment and institutional commitment; past experience and/or willingness to participate as a collaborating research partner in network activities, including the collection of timely, consistent, standardized core data and reporting of all de-identified information to a central SCC for the purpose of supporting pooled analyses; additional information regarding expertise and resources (i.e., access to existing data sets, access to large relevant patient samples, experience in assessment methods and technologies, institutional resources etc.) positioning the applicant to be an important contributor to the collaborative network. Applicants may have very strong, specific expertise – for example, in assessing a particular variable or construct, or may have broad expertise with a wide population. Explicit statements of the type and breadth of expertise relevant to the objectives of this RFA are strongly encouraged

o An estimate of the budget, with justification, required for the PRS' participation in the network activities proposed.

Applications should be flexible enough to accommodate further refinement and integration with the other awardees. Potential applicants at single research institutions

may coordinate with each other to meet minimum accrual targets and may submit common applications.

Budget Requirements for PRS Applications:

Investigators should prepare separate budgets for the independent and proposed PROMIS research for their own site(s), not for the entire network. PRS applicants should request a project period of 5 years. The total combined costs (direct and applicable facilities and administrative costs) of the independent and collaborative network projects may be up to $875,000 per year. Funding for independent projects may be requested for up to $450,000 total costs per year.

PRS applicants should provide a detailed budget for the independent project, and include the lump sum for network activities in the "Other" category of the overall budget. Details of this estimated network budget should be included following the Research Plan of the network concept proposals. The network portion of awarded funds for each U01 will be restricted pending approval of PROMIS projects by the Steering Committee. Once the Steering Committee has approved network projects, network funds may be reallocated across years or among sites as necessary. Continuation and level of funding for each PRS will be based on actual recruitment and overall performance. Awards will be subject to annual administrative review.

A minimum of 25% effort for the PI at each PRS is required, and should be represented in the independent project budget. The budget for proposed PROMIS collaborative project activities should include travel costs for two people to attend approximately four trips each year to attend Steering Committee meetings in Bethesda, MD, and other travel related to network operations (such as site visits), with appropriate justification.

Specific Instructions for SCC Applications

A separate complete application is required from institutions applying to serve as the Statistical Coordinating Center for PROMIS. SCC applicants are not required to be a network PRS, but PRS applicants may submit an application to serve as the SCC.

The sources of data for this research effort will be diverse; integrating data from these multiple sources may require development of novel data collection and editing systems. Therefore, one key function of the SCC will be to develop automated systems to ensure high quality, efficient reporting of data from individual PRS sites to the SCC for eventual use in pooled analyses. The SCC will also support and assist the PRSs in their development of standardized, automated data collection methods tailored to their local environments, to ensure that data are of uniformly high quality. The SCC and the Steering Committee will select one or more approaches to analyze data and construct item banks. The SCC will develop and conduct pilot testing of the software for computerized adaptive testing. In addition, the SCC will take the lead in developing education material or approaches for clinical researchers who will use the item banks and CAT system. SCC applicants must include a statement of willingness to work

collaboratively after award with the other funded sites to prepare a joint dissemination plan.

Applicants for the SCC should describe how the information technology needs of the network (data storage, curation, analysis, and retrieval) will be met and propose plans and methods with respect to coordination activities, including:

o Plans for working with PRSs to develop quality control procedures for data collection, storage, and transmission; plans for data management, including formatting, and documentation of core data elements using data dictionaries. The applicant should provide evidence of understanding and experience in creating a central data repository;

o Plans for a process to select items and domains for inclusion in pilot studies and in full-scale network data collection;

o Procedures to ensure data security, privacy, and confidentiality. When relevant, specific state and/or federal laws and their impact on the project must be fully explained;

o Plans and procedures for coordinating and maintaining regular communications among all the PRSs on an ongoing basis;

o Software standards to be used at the data and computer level;

o Methods for reporting the status of data submitted for pooled data analysis in terms of completeness and utility for pooled analysis;

o Plans for collaborating with PRSs as appropriate to identify or develop psychometric and statistical methods, and commitment to providing leadership in advancing psychometric, statistical, and outcomes methodologies;

o Scientific data software to be used, and approach to enabling users to visualize data, work across different platforms, collaborate, and analyze data both within and across data files;

o Plans for a data query infrastructure to allow for data storage and query over the lifetime of the network and beyond;

o Plans and procedures to: determine whether items perform differently in different populations (i.e., differential item functioning, DIF) and how to control for DIF when items are relevant for certain populations; select items to be included in item banks; identify the most appropriate IRT model or alternative; and develop and test a computerized adaptive testing system using the item banks created;

o Plans to develop a PRO computerized system that administers questionnaires, collects and summarizes data, and provides instant reports to the respondent, researchers, and health providers;

o Plans to facilitate public access to, and support for, the PROMIS, which includes but is not limited to: the item banks, short-form instruments, CAT system, and supporting material.

In addition to its central role in moving the network towards comparable data collection, the SCC is intended to accomplish several other research objectives with this initiative, particularly the support and advancement of statistical methodology for studies of process-outcome linkages in chronic disease care. Statistical analysis of pooled data is the joint responsibility of investigators from PRSs and the SCC. However, the SCC applicant should demonstrate familiarity with key statistical concepts relating to the analysis of population-based data, such as repeated measures analysis, missing data, hierarchical modeling, and variability across populations, facilities, and providers. The SCC should demonstrate psychometric expertise in the use of IRT models and other psychometric and statistical approaches to construct item banks, and in psychometric and software aspects of developing computer adaptive testing. The SCC should demonstrate the ability and flexibility to model data using a variety of IRT models to allow researchers to determine the optimal model for purposes of this study. SCC applicants should discuss the development of an infrastructure for supporting and furthering the development of psychometric and statistical methods in collaboration with researchers at the PRSs. Similarly, the SCC applicants should discuss the infrastructure for supporting, developing, and testing the computer adaptive testing systems in patient populations at the PRSs.

The research plan is limited to no more than 25 pages, and should use the following topic headings:

1. Research objectives and aims
    a. Item Bank Development
    b. Computer Adaptive Testing Development
    c. PRO Assessment, Data Collection, and Reporting System
2. Background and Significance
3. Data management, training, and quality control
4. Data analysis including psychometric and statistical methodologies
5. Communication
6. Scientific leadership and dissemination

Budget Requirements for SCC Applications:

SCC applicants should request a project period of 5 years with total costs (direct and applicable facilities and administrative costs) of up to $1,500,000 per year. For budget purposes, applicants should assume that in the first year all administrative aspects of PROMIS will be organized and enrollment started on at least one protocol. For each subsequent year, applicants may assume at least two active protocols. Costs for site visits to each of the PRSs should be included (assume up to four PRSs). A portion of awarded

funds for will be restricted pending approval of PROMIS projects by the Steering Committee. Continuation and level of funding will be based on actual recruitment and overall performance. Awards will be subject to annual administrative review.

General Instructions for All Applications

Because the Terms and Conditions of Award will be included in all awards issued as a result of this RFA, it is critical that each applicant include specific plans for responding to these terms. Plans must describe how the applicant will comply with NIH staff involvement as well as how all the responsibilities of awardees will be fulfilled.

Each applicant must describe the proposed duties and attendant qualifications for all other proposed personnel, such as project managers, psychometricians, statisticians, survey experts, HRQOL experts, data managers, computer programmers, and data entry clerks. Each applicant must have a defined space for administrative activities and administrative personnel that will serve as a focus for data management, quality control, and communication.

**USING THE RFA LABEL:** The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

**SENDING AN APPLICATION TO THE NIH:** Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies, in one package to:

Center For Scientific Review
National Institutes Of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

**APPLICATION PROCESSING:** Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

**PEER REVIEW PROCESS**

Upon receipt, the NIH will review applications for completeness and responsiveness. Incomplete and/or unresponsive applications will not be reviewed.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIH in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a written critique
o Receive a second level review by an appropriate National Advisory Council or Board.

**REVIEW CRITERIA**

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals.

For each PRS application, the independent research project will receive a score, the concept proposals will receive a score, and the overall application will receive a score. SCC applications will receive one overall score. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

o Significance
o Approach
o Innovation

o Investigator
o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

**SIGNIFICANCE:** Does this study address the general and specific research objectives of the RFA? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

**APPROACH:** Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

**INNOVATION:** Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

**INVESTIGATOR:** Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

**ENVIRONMENT:** Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

**ADDITIONAL REVIEW CRITERIA:** In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

**PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK:** The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

**INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH:** The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

PRS Independent Projects: To deserve a high priority score, the application must be judged clearly related to the general goal of providing clinical researchers with better tools or methods to measure patient-reported outcomes, and relevant or complementary to one or more of the specific objectives of this RFA.

PRS Network Concepts: The following factors will be considered in evaluating the merit of proposed network activities:

o Are the concept proposals clearly related to the specific aims of the RFA and the long-term goal of providing clinical researchers with better tools and methods to measure patient-reported outcomes?

o Is a heterogeneous patient population available, and are plans to include racial and ethnic minorities and subgroups appropriate for the scientific goals of the research adequate?

o Does the applicant adequately address the protection of patient information and confidentiality?

o Is there evidence of a supportive institutional environment for the proposed PRS? Does the proposed PRS utilize available resources well? Is there support and commitment from the institution?

o Do the research team and institution show clear promise of ability to work effectively as part of a collaborative network?

Statistical Coordinating Center

The following additional factors will be considered in evaluating the scientific merit of applications for the SCC:

o Do the qualifications and research experience of the Principal Investigator and staff include a track record of collaborative interdisciplinary activity, particularly in terms of coordinating large data collection? Does the project team have adequate expertise in

conducting pooled data analysis using IRT and in other psychometric, statistical and survey methods?

o Is the information technology to be used adequately described and appropriate to accomplish the objectives of the network?

o To what degree are the proposed technology and approach appropriate for clinical research and likely to have utility in a clinical setting?

o Does the applicant adequately address the protection of patient information and confidentiality?

o Are the plans for dissemination of the CAT tool adequate? Will this instrument be accessible and user-friendly?

## ADDITIONAL REVIEW CONSIDERATIONS

**Budget:** The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

**Data Sharing and Data Access:** The scientific review group will evaluate the adequacy of the proposed plan for sharing and data access. Comments on the plan and any concerns will be presented in an administrative note in the Summary Statement. The adequacy of the plan will be considered by NIH program staff and will be important in determining whether the grant shall be awarded. The sharing plan approved by program staff, after negotiation with the applicant when necessary, will become part of the terms and conditions of the award. NIH program staff will evaluate the compliance with the sharing plan and scientific progress in the non-competing continuation of the grant award application.

## RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: February 22, 2004
Application Receipt Date: March 22, 2004
Peer Review Date: July 2004
Council Review: September 2004
Earliest Anticipated Start Date: September 2004

## AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds

o Programmatic priorities.

**REQUIRED FEDERAL CITATIONS**

**HUMAN SUBJECTS PROTECTION:** Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.
http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

**DATA AND SAFETY MONITORING PLAN:** Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

**INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH:** It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or applications and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

**INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:** The NIH maintains a policy that children (i.e., individuals

under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

**REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS:** NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

**PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:**
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

**STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:**

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

**URLs IN NIH GRANT APPLICATIONS OR APPENDICES:** All applications and applications for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

**HEALTHY PEOPLE 2010:** The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

**AUTHORITY AND REGULATIONS:** This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health
and Human Services


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